AMENDMENTS TO THE SPECIFICATION

Before the Claims, please enter the previously filed Sequence Listing to the specification and renumber the pages.

Page 1, after the title, please add the following new paragraph:

CROSS-REFERENCE TO RELATED APPLICATIONS

[0000] This application is a continuation of serial number 09/813,156 filed on March 21, 2001 which is a continuation of serial number 08/991,862 filed on December 16, 1997, now U.S. Patent number 6,309,826 issued on October 30, 2001, which is a continuation-in-part of serial number 08/863,079 filed on May 23, 1997 now abandoned.

Page 4, replace paragraph [0012] with the following:

[0012] A further object of the invention is to provide methods for treating diseases associated with a defect in GP88 quantity or activity such as but not limited to cancer in ~~a mammal~~ mice or humans.

Page 14, replace paragraph [0062] with the following:

[0062] FIG. 8 shows the nucleotide and deduced amino-acid sequence of mouse GP88 (SEQ ID NOS 1 & 2, respectively). Peptide regions used as antigens to raise anti-GP88 antibodies K19T and S14R are underlined. The region cloned in the antisense orientation in the pCMV4 mammalian expression vector is indicated between brackets.

Page 15, replace paragraphs [0063] and [0065] with the following:

[0063] FIG. 9A shows the nucleotide sequence of human GP88 cDNA (SEQ ID NOS 16 & 17, respectively). Indicated between brackets is the region cloned in the antisense orientation into the pcDNA3 mammalian expression system; and

[0065] FIG. 10 shows the amino-acid sequence of mouse GP88 (SEQ ID NO: 2) arranged to show the 7 and one-half repeats defined as granulins g, f, B, A, C, D and e (right side). This representation shows that the region K19T and S14R used to raise GP88 antibodies for developing anti-GP88 neutralizing antibodies is found between two epithlin/granulin repeats in what is considered a variant region. Indicated on the right hand side is the granulin classification of the repeats according to Bateman et al (6). Granulin B and granulin A are also defined as epithelin 2 and epithelin 1 respectively according to Plowman et al., 1992 (5).

Page 52, replace paragraph [00158] with the following:

[00158] The conditioned medium (2000 ml) from PC cells was diluted with the same volume of H_2O and loaded on a 2.5 ml heparin-sepharose CL-6B column equilibrated in 10 mM sodium phosphate buffer pH 7.4 containing 75 mM NaCl (Pharmacia, Uppsala, Sweden). The column was washed with at least 10 bed volumes of the same equilibration buffer followed by a wash with 10 mM sodium phosphate buffer containing 0.15 M NaCl. The fraction containing GP88 was eluted with 5 bed volumes of 0.4 M NaCl, 10 mM Tris-HCl, pH 7.5. The eluate was stored at -20 C for further purification. A synthetic peptide K19T (SEQ ID NO: 3) (sequence: KKVIAPRRLPDPQILKSDT) was used to raise the antisera against the GP88 used in the immunoaffinity step. The K19T peptide was linked to CNBr-activated Sepharose 4B according to the method provided by the manufacturer (Pharmacia, Uppsala, Sweden). The specific anti-K19 antibody was purified using the K19T peptide affinity column by elution at acidic pH. Specifically, anti-K19T IgG was applied to a K19T peptide-Sepharose 4B column equilibrated with 10mM sodium phosphate buffer pH 6.5 (Buffer A) at a flow rate of 0.8 ml/hr, and circulated at 4°C overnight. After washing the column with 7 ml of Buffer A, the conjugate was eluted with 1 ml of HCl, pH 2.9, then 1 ml of HCl, pH 2.5 at a flow rate of about 0.1 ml/min in a tube containing 0 1 ml of 1M sodium phosphate buffer pH 7.0 to neutralize the pH. The concentration of affinity-purified IgG was determined by the absorbance at 280 nm.

Page 54, replace paragraph [00161] with the following:

[00161] Peptides corresponding to various regions of mouse and human GP88 were synthesized and conjugated to keyhole limpet Hemocyanin (KLH) by the "glutaraldehyde method." Peptide KLH conjugate was injected into chinchilla rabbits to raise anti-GP88 antibody. Two peptides, K19T and S14R, listed below, were found to generate neutralizing antibodies. Equivalent regions such as E19V of the human GP88 amino acid sequences were used to develop neutralizing anti-human GP88 monoclonal antibodies. Peptides were as follows:

P12T (SEQ ID NO: 4) from P208 to T219	PDAKTQCPDDST
K19T (SEQ ID NO: 3) from K344 to T362	KVIAPRRLPDPQILKSDT
S14R (SEQ ID NO: 5) from S562 to R575	SARGTKCLRKKIPR
E19V (SEQ ID NO: 6) (human GP88)	EKAPAHLSLPDPQALKRDV
A14R (SEQ ID NO: 7) (human GP88)	ARRGTKCLRREAPR

Page 58, replace paragraph [00171] with the following:

[00171] The presence of the antisense cDNA construct is tested by PCR analysis of genomic DNA of transfected clones using as primers an oligonucleotide located in the CMV promoter (SEQ ID NO: 8) (5'-CCTACTTGGCAGTACATCTACGTA-3') and the other corresponding to the start codon of GP88 cDNA (SEQ ID NO: 9) (5'-CGAGAATTCAGGCAGACCATGTGGGTC-3'). These primers would amplify a 551 bp DNA fragment from genomic DNA of transfected cells containing the antisense DNA construct described above.

Page 59, replace paragraph [00174] with the following:

[00174] The presence of the antisense construct in the transfected cells was determined by PCR analysis of their genomic DNA using as sense primer SP647 (SEQ ID NO: 8) (5'-CCTACTTGGCAGTACATCTACGTA-3') corresponding to CMV promoter region and antisense primer SP7 (SEQ ID NO: 10) (5'-CGAGAATTCAGGCAGACCATGTGGGTC-3') corresponding to start codon region of GP88. The sense primer SP647 and antisense primer AP912 (SEQ ID NO: 11)

(5'-CTGACGGTTCACTAAACGAGCTC-3') both located in the CMV4 promoter were used to test whether CMV promoter was inserted into the genomic DNA of control transfectants which had been transfected with empty pCMV4 vector.

Page 63, replace paragraphs [00186] and [00187] with the following:

[00186] A-hGP88: (SEQ ID NO: 12)
5'-A10GGATCCACGGAGTTGTTACCTGATC-3' (position nt: 362-344)

[00187] H-hGP88: (SEQ ID NO: 13)
5'-A10GAATTCGCAGGCAGACCATGTGGAC-3'(position nt: -12 to +8)

Page 64, replace paragraph [00190] with the following:

[00190] An alternative method to transfection of antisense cDNA is to use antisense oligonucleotides. It is known in the art that sequences around the translation initiation site (ATG encoding the first methionine) provide good sequences for efficient antisense activity. Secondly, sequences with an adequate GC content and that start with either a G or a C have increased efficiency and stability in forming a hybrid with corresponding sense sequence (32, 37, 38). Based on this rationale, it is anticipated that the following two sequences will be efficacious as antisense oligonucleotides to human GP88. The first one is a 22-mer named HGPAS1 starting 11 nucleotides upstream of the first ATG (methionine codon): HGPAS1 (SEQ ID NO: 14) (22): 5'-GGGTCCACATGGTCTGCCTGC-3'. The second oligomer is a 24 mer named HGPAS2 (24) located 21 nucleotides 3' (downstream) of the first ATG: HGPAS2 (SEQ ID NO: 15) (24):5'-GCCACCAGCCCTGCTGTTAAGGCC-3'. Other oligonucleotide antisense sequences can be explored by those of ordinary skill given the teachings herein. To judge the efficacy of a sequence to inhibit GP88 expression, oligonucleotides will be added to breast carcinoma cells in culture or any other human cell types under study in increasing doses. Cells will be collected at various time points (12 hours to several days) to measure the level of expression of GP88 protein by Western blot analysis or EIA using an antihuman GP88 antibody, using techniques known to those of ordinary skill in the art. Control cells will be treated with a nonsense or a sense oligomer.